Kidney International, Vol. 44 (1993), pp. 622–629

Urea kinetics during hemodialysis measured by microdialysis—A novel technique

GEORGE S. METRY, PER-OLA ATTMAN, PETER LÖNNROTH, SOHEIR N. BESHARA, and MATTIAS AURELL

Department of Nephrology and Department of Medicine, University of Göteborg, Göteborg, Sweden

Urea kinetics during hemodialysis measured by microdialysis—A novel technique. A microdialysis technique has been developed for estimation of concentrations of low molecular size compounds in the interstitial fluid *in vivo*. With this technique urea kinetics in the interstitial fluid and plasma were studied in ten patients during and after hemodialysis. There was a close correspondence between urea measurements in plasma and interstitium during hemodialysis. Urea rebound occurred in plasma during two hours after dialysis (15.8 ± 6.5% in the first hour and 11.8 ± 5.9% in the second hour). The urea rebound in the interstitium was delayed about 60 minutes after that of plasma (2.8 ± 8% and 14.1 ± 7.8% in the first and second hours, respectively) and continued for up to four hours after dialysis. The relationship between plasma urea rebound and the efficiency of hemodialysis and ultrafiltration volume was studied in 17 patients. Results showed a close relation between the fractional urea removal during dialysis and the plasma urea rebound. The contribution of *de novo* urea genesis to the rebound was estimated from the interdialytic increase in plasma urea concentrations, and was 17 to 24% of the plasma urea rebound during two hours postdialysis. The initial plasma urea rebound could in part result from urea influx to plasma from the enterohepatic recirculation of urea nitrogen. Plasma urea rebound should be taken into account for determination of the amount of dialysis delivered during hemodialysis.

Urea kinetics remains as one of the major laboratory parameters upon which the adequacy of dialysis therapy is evaluated [1]. Because urea is a highly diffusible molecule, its behavior during dialysis has been approximated by a single-pool model, which has been used over the past ten years to prescribe and individualize hemodialysis therapy [2]. This model assumes that during hemodialysis, equilibration of urea concentration gradients within the body occurs so rapidly that urea can be assumed to be removed from a single body fluid compartment (total body water).

The tissue microdialysis technique for measurements in the interstitial water space was first described by Delgado et al [3], and has since then been used mainly for neurobiological research in experimental animals [4]. Lönnroth, Jansson and Smith [5] have applied this technique in clinical studies for estimation of the subcutaneous interstitial concentrations of low molecular weight compounds, that is, glucose, lactate, glycerol and adenosine [reviewed in 6].

Direct measurements of intercellular urea concentrations during dialysis have not been performed in humans, because adequate methods have so far not been available. However, the microdialysis technique offers a means to study the urea kinetics at the intercellular interstitial space under non-steady-state conditions, that is, during and after hemodialysis.

Keshaviah et al [7] demonstrated that while urea distributes into total body water in acutely uremic dogs, its removal during dialysis is from a volume 12 to 14% less than that of total body water. Furthermore, a single pool model does not predict either the sharp drop in BUN at the beginning of dialysis or the postdialysis urea rebound [1]. Ilstrup et al [8] reported that a significant rebound (15% above post-treatment urea concentrations) was formed over a period of 60 minutes following discontinuation of hemodialysis. The rebound has been ascribed by the same authors to be due to intercompartmental redistribution of urea once external clearance is terminated. On the other hand, urea rebound has also been ascribed to increased urea generation rate due to increased protein catabolism [9], possibly as a result of patient membrane/dialysate interactions during hemodialysis [10]. In view of the aforementioned data, the single pool urea kinetic modeling was discredited, and the two-pool compartments model was proposed [7]. This model assumes that the body water is distributed in two pools, the intracellular fluid volume and the extracellular fluid volume. These pools and their respective sizes have physiological counterparts and are considered to be homogenous during dialysis, in order to allow mathematical modeling. The mass transport of urea between the compartments is then assumed to be linearly related to the concentration gradient.

Furthermore, since urea is generated mainly in the liver cells, and the liver is abundantly perfused with blood in relation to its volume, it may be assumed for ease of modeling that urea is released from the entire intracellular compartment [11]. Moreover, Rastogi et al [12] furthermore advocated that equilibration is rapid throughout the extracellular compartment with a negligible delay at the capillary wall, and that the main diffusional block for urea is at the cell wall.

In the present study we have focused on the urea kinetics in the extracellular compartment—plasma and interstitial fluid—during and after hemodialysis. The specific purpose of the study was to determine by tissue microdialysis the relationships

Received for publication June 18, 1992
and in revised form April 14, 1993
Accepted for publication April 15, 1993

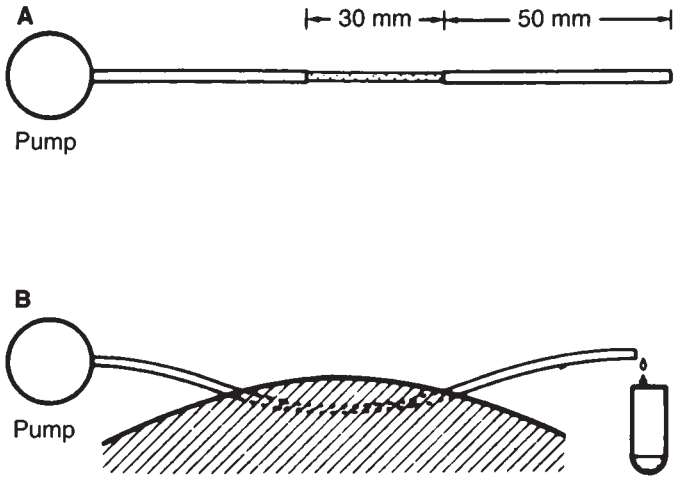

Fig. 1. *Schematic picture of the microdialysis probe (A).* The dialysis membrane is placed in the subcutaneous tissue while both the inlet and outlet are outside the skin (**B**). [After Lönnroth et al (1987).] A balanced solution is infused (perfusate) by pumps in the inlet (pump rate 2.5 μl/min). Microdialysate is collected from the outlet every 15 minutes and analyzed for urea concentrations. In the *in vitro* calibration procedures the probe is immersed in isotonic saline with different known urea concentrations (medium).

between urea transport in plasma and interstitial fluid in patients undergoing hemodialysis and to assess the postdialysis urea rebound phenomenon.

Methods

Study design

The investigation was performed in three separate studies:

(I) *In vitro* characterization and *in vivo* calibration of the microdialysis probe;
(II) Plasma and interstitial fluid urea concentrations during and after hemodialysis;
(III) Relationships between post-hemodialysis urea rebound and the efficiency of hemodialysis and ultrafiltration.

Microdialysis probe

A single cuprophane or polyamide (3000 molecular wt cut off) fiber obtained from standard hemodialysis (Cordis Dow, USA) or hemofiltration (Gambro F66, Gambro AB, Lund, Sweden) dialyzers was used. The fiber measured 30 × 0.3 mm and was glued at both ends to two polythene tubings (with an outer diameter of 0.5 mm) using cyanoacrylate glue and sterilized by ethylene oxide. The outlet of the polythene tubing had a standardized length of 50 mm and the inlet was connected to a precision pump (Sage Instruments, Boston, Massachusetts, USA; Fig. 1).

Study I

Characterization of microdialysis probe in vitro. The recovery of urea in the microdialysate by the probe from the surrounding medium was determined *in vitro*. The probe was placed in media with successively different urea concentrations: 2.5 mM, 5 mM, 20 mM, 30 mM and 40 mM. The probe was perfused with a 10 mM urea solution (perfusate) at a rate of 2.5 μl/min. Every fifteen minutes microdialysate samples (37.5 μl

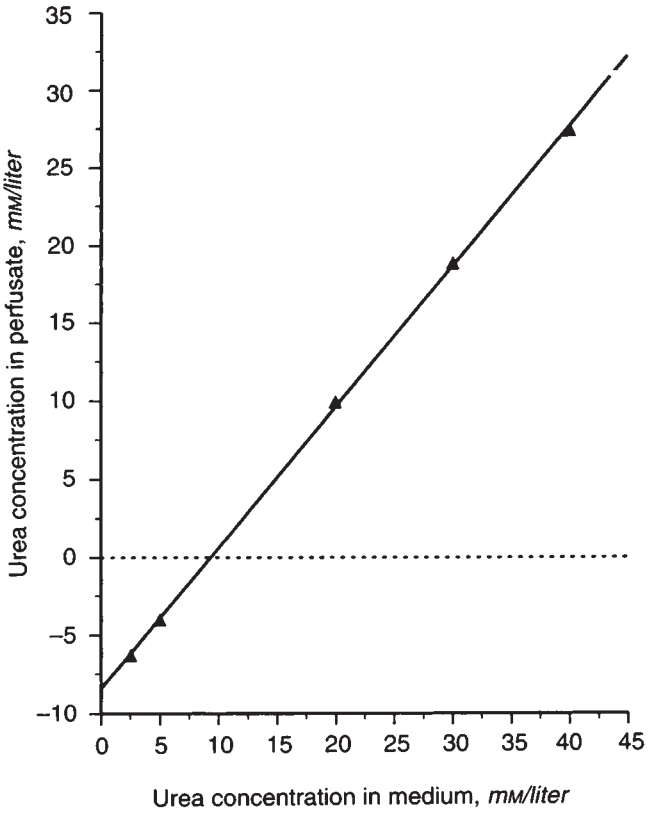

Fig. 2. *Characterization of the microdialysis probe* in vitro. Data are means of 3 consecutive experiments. A linear relation is formed between different media concentrations and the net change of urea concentration in the perfusate. 0 concentration change = the urea concentration in the infusate.

dialysate) was collected for every medium concentration used in collecting tubes. A linear relationship was demonstrated between urea concentration in the surrounding medium and net changed concentration in the microdialysate (Fig. 2). The percentage recovery of urea in the dialysate was constant (89 ± 3%).

The sensitivity of the probe to record rapid changes of urea concentration occurring in the surrounding medium was further studied by direct changing of the concentration of urea in the medium from 0 to 40 mM with normal saline as perfusate and collection of dialysate in three minute fractions. Fifty-five percent of the change in urea concentration was recorded in the dialysate after three minutes and 93% after six minutes, whereas 100% of recovery of the altered concentration (the steady state) was detected after seven to eight minutes (Fig. 3). The term "*membrane lag*" was introduced to describe the time required for the dialysate to reach the steady state concentration after changing the urea concentration in the medium. The "membrane lag" depended on the type of membrane used in the microdialysis probe and the substance to be measured. The "membrane lag" of the probes used in this study was approximately seven minutes (Fig. 3).

In vivo *calibration of the microdialysis probe.* To establish the recovery of interstitial urea concentrations by the probe *in vitro* we performed an *in vivo* calibration as described by Lönnroth et al [5], according to which varying concentrations of

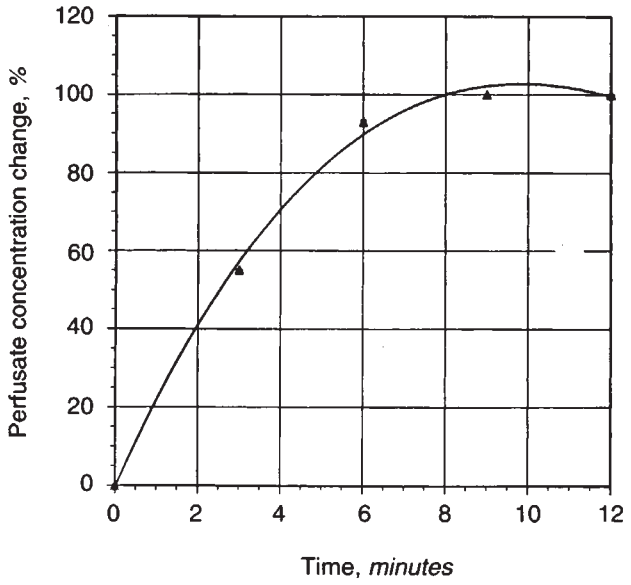

Fig. 3. *Change in urea concentration in the perfusate after rapid change of the ambient medium from 0 (0%) to 40 mM (100%).* Data are means of two consecutive experiments.

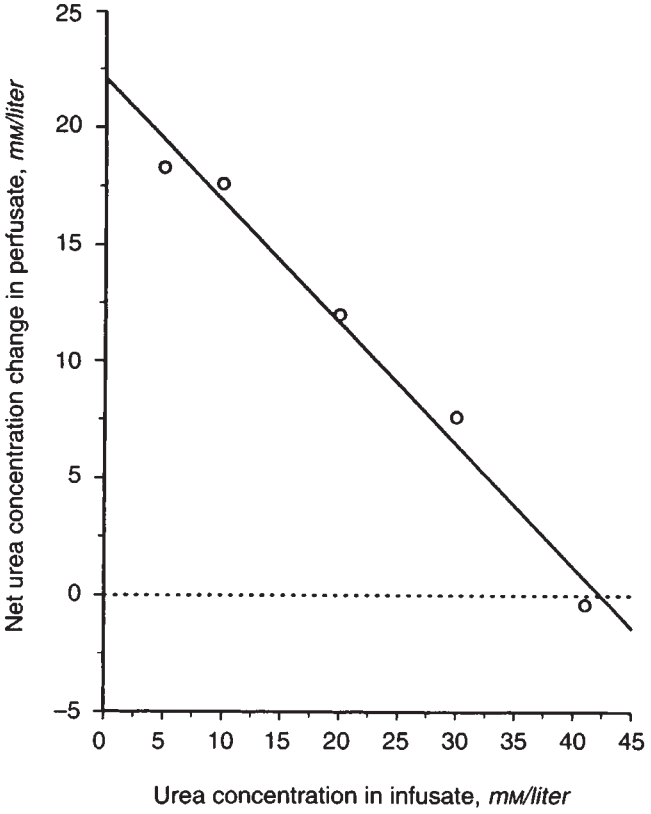

Fig. 4. In vivo *calibration of microdialysis probe in one of 4 experiments done with corresponding results.* A linear relation is formed between different concentrations of urea in the infusate and the net increase of urea in the perfusate. The 0 intercept on the X-axis indicates that urea concentration in the infusate is in equilibrium with the medium (= tissue concentration). The measured plasma urea concentration in this patient was 41.6 mM/liter and the calculated interstitial urea concentration was 42.5 mM/liter.

urea were infused in succession in the probe. The urea concentration of the perfusate that was equal to that of the collected dialysate, that is, when there was no difference between perfusate and dialysate urea concentrations, it was considered to be equal to that of the interstitial fluid and was assessed by regression analysis (Fig. 4). The calibration was performed in four patients with chronic renal failure and the technical procedure was as described below. The perfusate urea concentrations were 40 mM, 30 mM, 20 mM, 10 mM and 2.5 mM, respectively. Results of the *in vivo* calibrations are presented in Table 1. The order of urea concentrations infused was arranged in a non-consecutive manner to prevent alterations of the interstitial urea concentrations.

Plasma and interstitial urea measurements during hemodialysis (Studies II and III)

Patients. Twenty-one patients who were on regular hemodialysis treatments participated in the study. Their clinical characteristics are shown in Table 2. The patients who participated in the study were recruited from the outpatients' chronic hemodialysis department.

Ten patients (No. 1 to 10) participated in the microdialysis studies (studies II to III). Eleven additional patients (No. 11 to 21) participated in the studies of correlation between post-hemodialysis plasma urea rebound and hemodialysis efficiency and ultrafiltration (study III).

All patients gave their informed consent and the study was approved by the ethical committee of the University of Göteborg. The patients were studied during routine dialysis treatments using conventional hollow-fiber or parallel-flow dialyzers, bicarbonate-containing dialysis fluid and Gambro AK-10 or AK-100 dialysis equipment. The dialysis treatments were uneventful without significant or unexpected clinical or technical complications. Transient hypotension necessitating temporary reduction of the ultrafiltration rate was encountered in a few cases.

Table 1. Interstitial and plasma urea concentrations in four non-dialyzed patients with chronic renal failure

	Urea concentration *mM*	
Patient	Interstitium	Plasma
1	21.0	24.0
2	41.5	40.8
3	22.0	21.7
4	42.5	41.6

Interstitial urea concentrations were calculated from calibration of the microdialysis probe with perfusion of the probe with different concentrations of urea in the perfusate as described in the text.

Study II

Patients in series I were investigated according to the following: Six patients were studied during a four hour dialysis and a four hour postdialysis, while two patients were studied during a four hour dialysis and two patients during a three hour dialysis only.

Each patient lay in the supine position, and the dialysis probe

Table 2. Clinical characteristics of hemodialysis patients (HD)

	No.	Age	Sex	Blood pressure *mm Hg*	Body weight *kg*			Blood chemistry before HD			HD time *hours*	Duration RDT *years*
					Dry[c]	Before HD	After HD	Urea *mM/liter*	Creatinine *μM/liter*	Hb *g/liter*		
Series I[a]	1	67	F	115/65	63.5	65.9	63.6	34	830	93	4	2
	2	64	F	150/90	81.5	85.3	83	28	1085	76	4	2
	3	72	M	130/60	50	49.9	50	18	884	69	3	1.5
	4	64	M	155/80	77.5	80.4	78.4	32	927	79	4	1.5
	5	69	M	160/70	57	59.6	57.5	35	1169	100	4	6
	6	76	M	160/80	87	90.4	88.1	29	1105	99	4	6
	7	47	F	140/80	51	53.5	51.2	29	722	99	4	1.5
	8	67	F	115/60	64.5	67	65.7	35	758	94	4	2.5
	9	48	M	140/90	73.5	74.9	73.5	24.1	1168	97	4	1
	10	72	F	150/70	57.5	59.4	57.2	24.6	843	90	3	3
Series II[b]	11	74	M	145/65	57	60	57	31.2	935	121	4	0.5
	12	70	M	140/60	79.5	82.7	79.6	37.4	1064	75	4	3
	13	77	M	165/70	55	57.5	55.2	28	736	85	4	1
	14	70	F	140/70	46	47.3	45.8	24	1022	103	4	1
	15	73	F	160/80	57	58.8	56.9	33.7	74.1	110	3	3
	16	33	M	170/95	67	68.5	67.1	26.4	622	73	4	0.5
	17	46	F	170/90	93	95	93	52.3	128	88	4	3
	18	72	M	130/65	48.5	49.8	48.4	37	991	90	4	2
	19	35	F	130/70	49.5	53.7	53.2	23.9	716	94	4	0.5
	20	49	F	170/85	73.5	76.2	74.2	32.6	894	82	4	6
	21	77	M	150/70	82	87.3	83.6	38	959	93	4	1

[a] Series I, patients participating in tissue microdialysis study
[b] Series II, patients participated to study post-dialysis urea rebound; tissue microdialysis was not studied.
[c] Dry weight, estimated ideal post-dialysis weight.

was inserted in the subcutaneous tissue through a fine cannula below the umbilicus. The inlet of the polythene tubing was connected to the precision pump and perfused with normal saline containing 10 or 5 mM urea to prevent deprivement of interstitial urea [5]. The infusion rate was 2.5 μl/min. After an equilibration period of 30 minutes, blood was collected in an EDTA tube and 15-minute microdialysate was collected in a small tapered plastic tube. Hemodialysis was started and the microdialysate was collected in 15-minute fractions throughout dialysis and after dialysis according to the above scheme. Blood samples were collected every 15 minutes in the first hour of dialysis, and every hour throughout the rest of the dialysis and the postdialysis period. Blood samples were drawn from the arterial nipple during dialysis, and after dialysis they were taken from a dialysis cannula in the arteriovenous fistula. Transmembrane pressure (TMP), blood flow rate and blood pressure (BP) were registered hourly during dialysis, and the pre- and postdialysis body weight measured.

Study III

Sixteen patients participated in this study. Blood samples for determination of urea concentrations were obtained before and at the end of dialysis, at one and two hours after dialysis and before next dialysis. Body weights before and after dialysis as well as before next dialysis were recorded. The efficiency of urea removal during dialysis was expressed as the percentage of urea disappearance according to the following equation:

$$\text{per cent urea disappearance} = \frac{Co - Ct}{Co} \times 100$$

where Co = predialysis urea concentration and Ct = immediate postdialysis urea concentration.

Determination of urea generation rate

Ureagenesis was considered to take place at a constant rate and thus to result in identical urea concentrations in each compartment of body water. It was estimated from the rise in plasma urea concentration between two consecutive dialysis sessions from an initial concentration obtained two hours after the end of dialysis (C_{2hr}) to avoid any error due to rebound. Urea generation (Gu) was calculated according to Pedrini's formula [12]:

$$Gu = [(Vu + b_{tid})C_i - VuC_{2hr}]/tid$$

where b = rate of change in total body water, ml/u, estimated from changes in body weight; tid = interdialytic interval in hours; and C_i = next predialysis urea concentration. Vu was assumed to be 58% of dry body weight (Table 2).

Determination of urea concentrations

Urea concentrations in plasma, perfusate and microdialysis fluid were measured by an enzymatic colorimetric test applying a modified Berthelot reaction (Human Diagnostica, Germany).

Statistical methods

Statistical significance of differences was tested with Student's two-tailed *t*-test for paired data. Differences with a P value <0.05 were considered significant. Linear regression analysis was performed according to the least square method.

Results

In vivo *calibration (Study I)*

Calculation of interstitial urea concentration from the slope of microdialysate urea concentrations yielded an almost identical

Table 3. Urea concentrations (mean ± SD) in interstitial fluid and plasma during and after hemodialysis in ten patients

Sample no.	Time hours	Interstitial fluid	Plasma	P
		mmol/liter		
1	0 (start of dialysis)	30.0 ± 6.3	29.8 ± 6.4	NS
2	0.25	28.2 ± 6.7	27.0 ± 5.3	
3	0.5	25.6 ± 6.1	24.3 ± 5.3	
4	0.75	23.4 ± 5.0	22.3 ± 4.0	
5	1	22.0 ± 4.7	20.8 ± 4.3	NS
6	1.25	20.7 ± 3.6		
7	1.5	19.8 ± 3.1		
8	1.75	18.1 ± 2.9		
9	2	16.6 ± 2.5	16.4 ± 2.4.0	NS
10	2.25	16.0 ± 2.5		
11	2.5	14.9 ± 2.6		
12	2.75	14.2 ± 2.8		
13	3	13.6 ± 2.3	13.4 ± 2.1	NS
14	3.25	12.7 ± 2.0		
15	3.5	12.1 ± 2.1		
16	3.75	11.3 ± 1.9		
17	4 (end of dialysis)	11.5 ± 2.7	11.4 ± 1.9	NS
18	4.25	11.2 ± 2.6		
19	4.5	11.3 ± 2.5		
20	4.75	11.6 ± 2.4		
21	5	11.9 ± 2.9	13.2 ± 1.8	NS
22	5.25	12.7 ± 2.3		
23	5.5	12.8 ± 3.6		
24	5.75	13.1 ± 3.6		
25	6	13.4 ± 2.8	14.5 ± 1.8	NS
26	6.25	13.5 ± 2.6		
27	6.5	13.8 ± 2.9		
28	6.75	14.2 ± 3.3		
29	7	14.3 ± 3.4	14.7 ± 2.1	NS
30	7.25	14.4 ± 4.1		
31	7.5	14.6 ± 4.0		
32	7.75	14.9 ± 4.2		
33	8	15.0 ± 4.1	14.9 ± 2.0	NS

value to that of plasma urea concentrations indicating equilibrium of plasma and interstitial urea concentrations in steady state *in vivo* conditions (Table 1, Fig. 4).

Effect of hemodialysis on plasma and interstitial urea concentrations (Study II)

Table 3 and Figure 5 show that during the first hour of hemodialysis, there was a sharp drop in plasma urea levels (mean 30.2%), followed by a slower decrease during the rest of dialysis. At the end of dialysis, the mean plasma urea concentration was reduced by approximately 60%.

The interstitial urea levels decreased synchronously with those of plasma. During the first hour the mean reduction was 29.7% and reached 61.1% by the end of dialysis.

There was no significant difference between mean plasma and interstitial urea concentrations at any time during and after the end of hemodialysis (Table 3).

There was about 15 minutes lagging in the descent of interstitial urea curve behind that of plasma during the first three hours of dialysis (Fig. 5). This was attributed to the membrane barrier ("membrane lag") of the microdialysis probe, which induced a delay in recording the changes in urea turnover in the interstitium. During the fourth hour of dialysis the "membrane lag" was not apparent (Fig. 5).

Plasma and interstitial urea concentrations after hemodialysis—rebound of urea (Study III)

The plasma and interstitial urea concentrations were determined during four hours after dialysis. There was an increase of plasma urea concentrations during the four hours after dialysis. When expressed in percent of the urea concentration at the end of dialysis, the rebound of urea in plasma was most marked during the first hour after dialysis (15.8 ± 6.5%), declined during the second hour (11.8 ± 5.9%), and returned to low levels in the third and fourth postdialytic hours (2.8 ± 3.6 and 3.2 ± 1.6%; Fig. 5). On the other hand, the urea rebound in the interstitial fluid showed a different relation to time and was maximal during the second hour, (14.1 ± 7.8%) and continued during the third and fourth hours (8.8 ± 12 and 9.2 ± 4.9%). During the four hours post-dialysis there was about a 60 minute time lag between the plasma and interstitial urea concentration curves, with a significantly longer time to reach 50% of maximal urea rebound in the interstitial fluid (54 min vs. 114 min, $P < 0.005$).

The contribution of urea genesis to the plasma urea rebound during two hours post-dialysis was studied in ten patients (Table 4). The mean interdialytic urea generation rate was 0.25 ± 0.08 mM/liter body water/hr and constituted mean 17.2 ± 6.5% of plasma urea rebound in the first hour and 23.6 ± 9% in the second hour after dialysis. The correlation between urea removal and rebound is demonstrated graphically in Figure 6.

There was a significant correlation between the fractional plasma urea reduction during dialysis and the fractional plasma urea rebound in the first ($r = 0.67$, $P < 0.01$) and second hour ($r = 0.74$, $P < 0.01$) in the 17 patients studied during and after dialysis (Fig. 6). However, there was no significant correlation between the fractional reduction of body water and the plasma urea rebound.

Discussion

Results of the present study demonstrate that the microdialysis technique is well suited to evaluate the urea concentrations in the interstitial fluid *in vivo* and to closely monitor the concentration changes during and after dialysis. The *in vivo* calibration results show that there is a complete equilibrium of urea concentrations in plasma and interstitium in the nondialyzed uremic patient.

Concern may be raised about the potential for depletion of urea within the tissue compartment during the study. To prevent this the perfusate fluid contained 10 or 5 mM urea. If a depletion had occurred, a consistent decline of interstitial urea concentrations might have been expected after dialysis. In contrast, there was a continuous increase of interstitial urea concentrations after dialysis, and furthermore, after four hours post-dialysis the plasma and interstitial urea concentrations were identical. In addition, during the *in vitro* experiments and in the *in vivo* calibration studies without hemodialysis, the relationships between the urea concentrations in the perfusate and the net change of urea was strictly linear, excluding a depletion of interstitial urea when perfusate concentrations of urea >1 mM were used.

During dialysis, there was a tantamount decrease of urea concentration in plasma and interstitium. This finding demonstrates that urea equilibrates between subcutaneous interstitial

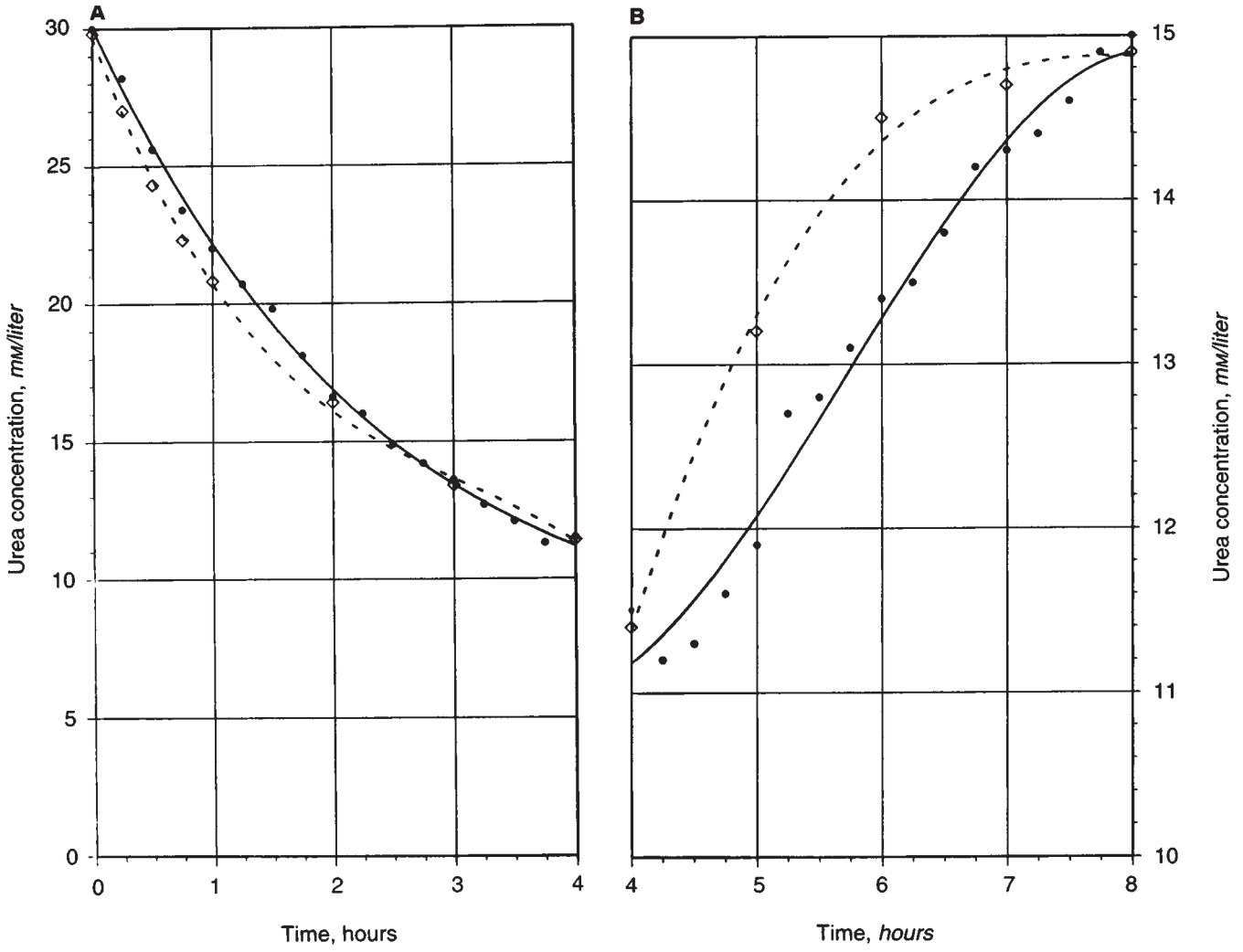

Fig. 5. *Mean interstitial and plasma urea concentrations (mean ± SD) during hemodialysis (A) and during four hours after dialysis (B).* Symbols are: (•——•) interstitial fluid; (◇----◇) plasma.

fluid and plasma so rapidly that similar levels in both compartments are maintained during dialysis (Table 3, Fig. 5). The time lag of 15 minutes between plasma and interstitial urea concentration curves during dialysis is most likely due to the membrane lag of microdialysis catheter and to a minute diffusional delay through the capillary walls. Therefore, plasma and interstitial fluid can be considered to be in equilibrium for urea before and during dialysis. However, this relation may temporarily be altered during the first hours after dialysis when rebounds of plasma urea concentrations are found.

We found that the net urea rebound in plasma, that is, the increase of urea concentrations in excess of the mean interdialytic rise in urea concentrations, was maximal during the first hour after dialysis and was completed during the second hour. Pedrini, Zereik and Rasmy reported that the net urea rebound was stabilized already within 50 minutes after dialysis [13]. This quantitative discrepancy is not readily explained, but could possibly in part be related to differences in dialysis procedures

Table 4. Interdialytic urea generation rate in ten hemodialysis patients

Patient	C_{2hr}	C_i	Vu	tid	Gu
	mM/liter		*liter*	*hours*	*mM/liter/hr*
1	13.2	35.2	43.2	91	0.28
2	15.5	35.6	33.1	89	0.25
3	12.1	18.1	31.9	43	0.16
4	13.9	35.9	33.1	66	0.38
5	6.3	18.1	26.1	66	0.18
6	8.8	21.0	28.1	42	0.34
7	13.6	28.4	38.9	90	0.18
8	30.2	48.5	53.9	66	0.31
9	9.7	16.1	27.4	40	0.16
10	15.6	27.0	28.1	44	0.28
Mean	13.9	28.4			0.25
SD	6.5	10.4			0.08

Abbreviations are: C_{2hr}, plasma urea concentration 2 hr post-dialysis; C_i, plasma urea concentration before next dialysis; Vu, 58% of dry body weight; tid, interdialytic time; Gu, urea generation rate.

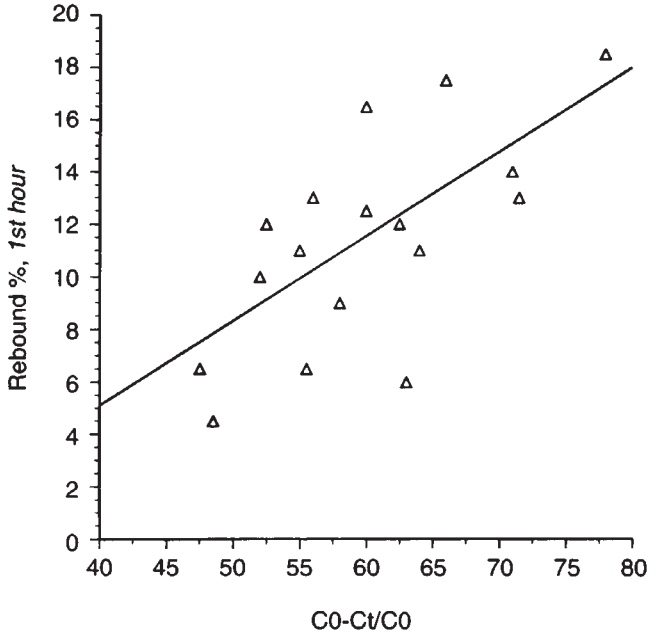

Fig. 6. *Correlation between fractional reduction of urea in plasma during dialysis* ($\frac{Co-Ct}{Co}$) *and the first hour post-dialysis fractional plasma urea rebound in 17 hemodialysis patients* ($r = 0.67$, $P < 0.01$).

and urea removal during dialysis, as well as variations in urea generation from food intake in the initial phase of dialysis.

The plasma urea rebound has been attributed to the multiple pool nature of the human body [11], together with the presence of a diffusional barrier at the cell wall [12]. This delays the equilibration of urea concentrations and creates an imbalance between intracellular and extracellular compartments immediately after dialysis, to be followed by an interpool re-equilibrium as originally described by Shackman et al [14].

The urea rebound amounts to 10 to 15% of postdialysis urea concentration, and should be taken into consideration when assessing efficiency or adequacy of different hemodialysis regimens based on calculations of urea kinetics from pre- and post-dialysis urea concentrations. To avoid the confounding influence of urea rebound, the plasma urea curve in Figure 5b indicates that post-dialysis urea concentrations should ideally be determined in plasma obtained not earlier than two hours after dialysis. By that time plasma and interstitial urea concentrations are approaching equilibrium with little continuing interstitial urea rebound. However, the equilibration between the intracellular and extracellular compartments may not be completed until several hours later [14].

In our study, urea rebound occurred synchronously in the interstitium, but with about 60 minutes lagging of the interstitial fluid rebound curve behind that of plasma, which by far exceeds the time of the membrane lag (Fig. 5b). This time lag could not be attributed to the membrane barrier of the microdialysis probe, being approximately seven minutes, as shown in the *in vitro* calibration experiments. Instead, our data indicate that rebound is present in plasma prior to the rebound in the interstitium. To explain this finding we envisage another extracellular pool to be a source of plasma urea rebound, that is, urea in the portal circulation. Walser and Bodenlos [15] showed that 15 to 30% of urea synthesized in a normal subject is catabolized endogenously by enteric bacterial urease. However, this degradation of urea does not result in a net loss of urea from the body, since the nitrogen derived from urea re-enters the blood compartment through the enterohepatic circulation, and is reconstituted back into urea. Jones et al [16] further demonstrated that the enterohepatic circulation of urea nitrogen is 2.5 to 4 times greater in uremic patients than in normal subjects, probably as a consequence of greater availability of urea substrate together with an increase of bacterial urease activity in the intestine. Based on the present data it could be assumed that an increased turnover in the enterohepatic circulation could contribute to the plasma urea rebound. It is, however, beyond the scope of this investigation to evaluate this hypothesis. Ultimately, we assume that the rebound phenomenon is the result of a post-dialysis re-equilibration process between the intracellular compartment and the extracellular compartment, as well as between the enterohepatic urea circulation and the systemic circulation and the extracellular compartment.

In addition, some studies have provided evidence for an accelerated protein catabolism during and after dialysis to replace amino acid and glucose losses in the dialysate [17]. Protein hypercatabolism may furthermore result from a blood-membrane/dialysate interaction, possibly through induction of interleukin-1 [10, 17, 18]. However, the contribution of these factors for the post-dialysis urea rebound remains to be determined.

The results of our study confirm that there is a significant correlation between the efficiency of urea removal during dialysis and the magnitude of urea rebound (Fig. 6). This finding is in good agreement with that of Pedrini et al [13], who reported a correlation between K_t/V and the urea rebound percentage.

In summary, the microdialysis method appears to be a useful means to measure the interstitial urea concentration during hemodialysis provided that *in vitro* characterization and *in vivo* calibration of the probe is adequately done. During hemodialysis urea concentrations equilibrate rapidly between interstitium and plasma. Measurements of plasma urea concentrations therefore provide a good expression of the concentrations in the interstitial fluid before and during dialysis. It remains, however, to be explored whether the determinations in the abdominal subcutaneous interstitium are representative of the entire interstitial compartment.

The post-hemodialysis urea plasma rebound phenomenon can be considered as a re-equilibration process between multiple body pools and extends for about two hours after hemodialysis. The magnitude of rebound is strongly influenced by the efficiency of the dialysis procedure and should be recognized when evaluating the dose of dialysis delivered to patients.

Acknowledgments

This study was supported by John & Brit Wennerströms Research Fund for Kidney Diseases and the Kidney Patients Foundation of Western Sweden. We also wish to thank the staff of the dialysis department for their help and Ms. Ann Stenman for preparing the manuscript.

Reprint requests to Prof. Mattias Aurell, Department of Nephrology, Sahlgrenska Hospital, S-413 45 Göteborg, Sweden.

References

1. Tsang HK, Leonard EF, LeFavour GS, Cortell S: Urea dynamics during and immediately after dialysis. *ASAIO J* 8:251–260, 1985
2. Sargent JA: Control of dialysis by a single pool urea model: The National Cooperative Dialysis Study. *Kidney Int* 23 (Suppl 13):S19–S25, 1983
3. Delgado JMR, Feudis FV, Roth RH, Ryugo DK, Mitruka BM: Dialytrode for long-term intravertebral perfusion in awake monkeys. *Arch Int Pharmacodyn Ther* 198:9–21, 1972
4. Ungerstedt U, Pycock C: Functional correlates of dopamine neurotransmission. *Bull Schweiz Akad Med Wiss* 1278:1–5, 1974
5. Lönnroth P, Jansson PA, Smith U: A microdialysis method allowing characterization of the intercellular water space in humans. *Am J Physiol* 253:E228–E231, 1987
6. Lönnroth P, Smith U: Microdialysis—A novel technique for clinical investigations. *J Int Med* 227:295–300, 1990
7. Keshaviah P, Ilstrup K, Shapiro W, Hanson G: Hemodialysis urea kinetics is not a single pool. (abstract) *Kidney Int* 627:165, 1985
8. Ilstrup K, Hanson J, Shapiro W, Keshaviah P: Examining the foundations of urea kinetics. *ASAIO Trans* 31:164–168, 1985
9. Borah MF, Schoenfeld PV, Gotch FA, Sargent JA, Wolfson M, Humphreys MH: Nitrogen balance during intermittent dialysis therapy of uremia. *Kidney Int* 14:491–500, 1978
10. Gutierrez A, Alvestrand A, Bergström J: Membrane selection and muscle protein catabolism. *Kidney Int* 42(Suppl 38):S-86–S-90, 1992
11. King PH, Baker WR, Ginn HE, Frost AB: Computer optimization of hemodialysis. *ASAIO Trans* 14:389–393, 1968
12. Rastogi SP, Frost T, Andersen J, Ashcroft R, Kerr DNS: The significance of disequilibrium between body compartments in the treatment of chronic renal failure by hemodialysis. *Proc Eur Dial Transplant Assoc* 5:102–112, 1968
13. Pedrini LA, Zereik S, Rasmy S: Causes, kinetics and clinical implications of post-hemodialysis urea rebound. *Kidney Int* 34:817–824, 1988
14. Shackman R, Chrisholm GD, Holden AJ, Pigott RW: Urea distribution in the body after hemodialysis. *Br Med J* 2:355–358, 1962
15. Walser M, Bodenlos LJ: Urea metabolism in man. *J Clin Invest* 38:1617–1626, 1959
16. Jones EA, Smallwood RA, Craigie A, Rosenoes VM: The enterohepatic circulation of urea nitrogen. *Clin Sci* 37:825–836, 1969
17. Farrel PC, Hone PW: Dialysis induced catabolism. *Am J Clin Nutr* 33:1417–1422, 1980
18. Shaldon S, Deschodt G, Branger B, Granolleras C, Baldamus CA, Koch KM, Lysaght MJ, Dinarello CA: Hemodialysis hypotension: The interleukin hypothesis restated. *Proc Eur Dial Transplant Assoc* 22:229–243, 1985